

## Relationship Between Residual Renal Function, Inflammation, and Anemia in Peritoneal Dialysis

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*In peritoneal dialysis (PD) patients, we analyzed the relationship between residual renal function (RRF) and well-known predictors of mortality such as anemia, inflammation, and nutrition. We also investigated possible associations between the foregoing parameters and cardiovascular comorbidity, peritoneal transport rate, statin and antihypertensive treatments, and ultrafiltration volume.*

*Our study enrolled 24 patients (17 men, 7 women; mean age:  $56 \pm 12$  years) who had started PD at our hospital between 1998 and 2004. Patients who had been hospitalized or had had peritonitis before the study were excluded. Nutrition status, inflammation, anemia, RRF, and dialysis adequacy were assessed after 1–2 months.*

*We found that RRF was positively correlated with normalized protein equivalent of nitrogen appearance (nPNA:  $r = 0.52$ ,  $p = 0.03$ ) and negatively correlated with C-reactive protein (CRP:  $r = -0.47$ ,  $p < 0.01$ ) and peritoneal ultrafiltration ( $r = -0.42$ ,  $p < 0.05$ ). Only the nPNA and CRP correlations remained statistically significant on multivariate logistic regression analysis (CRP:  $r = 0.8$ ,  $p = 0.011$ ; nPNA:  $p = 0.013$ ). Moreover, as compared with patients without inflammation, patients with inflammation had significantly lower hemoglobin (Hgb) levels ( $11.8 \pm 1.1$  g/dL vs.  $13.2 \pm 1.2$  g/dL,  $p < 0.02$ ), serum prealbumin levels ( $27.3 \pm 8$  mg/dL vs.  $36.6 \pm 9$  mg/dL,  $p < 0.05$ ), and serum transferrin levels ( $168 \pm 34$  mg/dL vs.  $202 \pm 31$  mg/dL,  $p < 0.05$ ), and a higher erythropoietin resistance index (ERI:  $10 \pm 4$  vs.  $6 \pm 3.5$ ,  $p < 0.02$ ). We observed no differences in RRF or nutrition status between the patients with high and with low peritoneal transport. Regarding comorbidity, patients with pre-existing cardiovascular disease had higher*

*CRP levels ( $0.8 \pm 0.4$  mg/dL vs.  $0.4 \pm 0.4$  mg/dL,  $p < 0.05$ ) and lower mean Hgb levels ( $13.3 \pm 1$  g/dL vs.  $14.4 \pm 1$  g/dL,  $p < 0.05$ ) than did patients without such pre-existing disease.*

*A strong, predictable association exists between RRF and inflammation and nutrition status in incident patients on PD. Serum CRP is a good indicator of inflammation, which correlates well with nutrition status, anemia, and responsiveness to erythropoietin therapy.*

### Key words

Residual renal function, nutrition, inflammation, anemia

### Introduction

As the ADEMEX study demonstrated (1), increases in peritoneal small-solute clearance had a neutral effect on patient survival, even when groups were stratified according to a variety of factors known to affect survival. Renal and peritoneal clearances were found not to be equivalent, because only residual renal function (RRF) had a beneficial effect on outcome and quality of life in the patients (2).

The reason or reasons that RRF, but not peritoneal clearance, is an important determinant of mortality are not yet clear. Several authors have observed that RRF may affect a patient's endocrine functions [for example, erythropoietin (EPO) production, vitamin D homeostasis, and phosphatemia (3)], volume control, and removal of middle molecules or low-molecular-weight proteins (4).

We investigated whether RRF has a relationship with well-known predictors of mortality such as anemia, inflammation, and nutrition status.

### Patients and methods

Our study enrolled 24 patients (17 men, 7 women; mean age:  $56 \pm 12$  years) who had commenced

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peritoneal dialysis (PD) at our hospital between 1998 and 2004. Patients were excluded if they had been hospitalized or had experienced a peritonitis episode before the start of the study. All enrolled patients were hypertensive, 79% had left ventricular hypertrophy, and 17% had diabetes. Of the 24 patients, 41% had at least one of the following conditions: coronary artery disease, cardiac failure, or peripheral vascular disease. The two most common causes of renal failure in this population were hypertensive nephrosclerosis (41%) and diabetic nephropathy (17%). Almost all patients (80%) were taking antihypertensive medications (with 63% taking angiotensin converting-enzyme inhibitors or angiotensin II receptor blockers), and 33% were taking statins. Within 1 – 2 months after PD start, the patients were assessed for nutrition status [albumin, prealbumin, cholesterol, transferrin, normalized protein equivalent of nitrogen appearance (nPNA)], inflammation [C-reactive protein (CRP), fibrinogen, haptoglobin, ferritin], anemia [hemoglobin (Hgb), erythropoietin resistance index (ERI) expressed as the ratio of the weekly EPO dose (in international units per kilogram) to Hgb concentration [in grams per deciliter]], RRF [creatinine clearance (CCr), diuresis volume], and dialysis adequacy (Kt/V, peritoneal equilibration test, ultrafiltration).

Biochemical blood parameters were analyzed using standard techniques. Immunonephelometry was used to determine CRP in milligrams per deciliter (normal range: <0.5 mg/dL; above-normal values are generally thought to indicate clinically significant inflammation). A 24-hour urine collection corrected to a body surface area of 1.73 m<sup>2</sup> was used to determine CCr.

Data were processed using the SPSS software package for Windows (version 14.0: SPSS, Chicago, IL, U.S.A.) and were expressed as mean  $\pm$  standard deviation. Parametric variables were analyzed using the Student *t*-test and bivariate correlation. Nonparametric variables were analyzed using the chi-square test. Regression models were used as appropriate. A *p* value less than 0.05 was considered statistically significant. Factors possibly determining RRF were evaluated by univariate (Pearson correlation and the Spearman test) and multivariate analyses (stepwise option within a linear regression and general linear models).

## Results

Table I shows the mean variables for the study patients. On univariate analysis, RRF was positively correlated with nPNA ( $r = 0.52$ ,  $p = 0.03$ ) and negatively correlated with CRP ( $r = -0.47$ ,  $p < 0.01$ , Figure 1) and peritoneal ultrafiltration ( $r = -0.42$ ,  $p < 0.05$ ). Only nPNA and CRP were statistically significantly correlated with RRF on the multivariate logistic regression analysis (CRP:  $r = 0.8$ ,  $p = 0.011$ ; nPNA:  $p = 0.013$ ; Table II).

Moreover, as compared with patients having normal CRP levels, patients with elevated CRP levels showed significantly lower Hgb levels ( $11.8 \pm 1.1$  g/dL

TABLE I Clinical characteristics of the patients

CCr (mL/min)	6.7 $\pm$ 4.2
Hemoglobin (g/dL)	12.6 $\pm$ 1.3
ERI [weekly IU $\cdot$ kg <sup>-1</sup> $\cdot$ (g/dL) <sup>-1</sup> ]	7.6 $\pm$ 4.2
CRP (mg/dL)	1.1 $\pm$ 1.8
Albumin (g/dL)	4.0 $\pm$ 0.4
Prealbumin (mg/dL)	32.7 $\pm$ 10.1
Daily nPNA (g/kg)	0.9 $\pm$ 0.3
Kt/V peritoneal	2.3 $\pm$ 0.9
Ultrafiltration (L/24 h)	1.1 $\pm$ 0.5

CCr = creatinine clearance; ERI = erythropoietin resistance index; CRP = C-reactive protein; nPNA = normalized protein equivalent of nitrogen appearance; Kt/V = dialysis adequacy index.

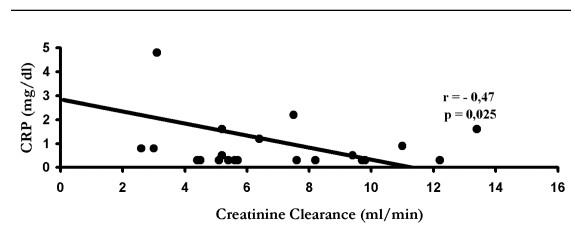


FIGURE 1 Correlation between creatinine clearance and C-reactive protein (CRP).

TABLE II Independent factors determining residual renal function

	$\beta$ Statistic	Standard error	<i>p</i> Value
CRP (mg/dL)	-0.544	0.397	0.014
Daily nPNA (g/kg)	0.515	2.130	0.019
Ultrafiltration (L/24 h)	-0.258	0.889	0.386

CRP = C-reactive protein; nPNA = normalized protein equivalent of nitrogen appearance.

vs.  $13.2 \pm 1.2$  g/dL,  $p < 0.02$ ), serum prealbumin levels ( $27.3 \pm 8$  mg/dL vs.  $36.6 \pm 9$  mg/dL,  $p < 0.05$ ), and serum transferrin levels ( $168 \pm 34$  mg/dL vs.  $202 \pm 31$  mg/dL,  $p < 0.05$ ), and a higher ERI ( $10 \pm 4$  vs.  $6 \pm 3.5$ ,  $p < 0.02$ ). Peritoneal transport showed no correlation with RRF or nutrition status.

With regard to comorbidity, patients with pre-existing cardiovascular disease (CVD) had higher CRP levels ( $0.8 \pm 0.4$  mg/dL vs.  $0.4 \pm 0.4$  mg/dL,  $p < 0.05$ ) and lower mean Hgb levels ( $13.3 \pm 1$  g/dL vs.  $14.4 \pm 1$  g/dL,  $p < 0.05$ ) than did patients without pre-existing CVD. Diabetes mellitus and drugs received had no influence on RRF or inflammation.

### Discussion

Throughout PD treatment of chronic renal failure, preserved or enhanced renal clearance has been associated with multiple beneficial effects. Several studies have demonstrated that RRF has an independent effect on morbidity and mortality outcomes in PD patients (2). This effect could be related to its contribution to solute and water excretion and its relationship to inflammation and nutrition status. The relationship between RRF and CRP is one of the most important findings of our study, consistent with findings in other studies (5) in which RRF and CRP have been found to be interrelated and to combine adversely to enhance mortality.

The negative correlation between RRF and CRP suggests that a reduction in renal function aggravates the inflammatory state through retention of proinflammatory mediators. Renal failure is associated with increases in inflammatory mediators, including CRP and interleukin 6, which may be the result of increased monocyte activation or impaired clearance of inflammatory mediators (6). Conversely, inflammation could exert negative effects on RRF as evidenced by a study showing a more rapid decline of RRF in the presence of inflammation (7).

Unlike Chung *et al.* (5), we found no correlation between RRF and peritoneal transport rate, probably in part because of our small sample size and cross-sectional study design.

Our findings show that RRF and nutrition are also related. Various authors have demonstrated the negative impact of declining RRF on dietary protein intake (8). Anorexia in PD patients is well established in relation to declining RRF, use of glucose and amino acid solutions, and inflammation.

Another important finding is that our patients with inflammation showed a higher ERI and worse nutrition than did patients without inflammation. The ERI has shown a strong positive relationship with inflammation and markers of nutrition in patients with advanced chronic kidney disease, and in those on hemodialysis or post transplant (9,10). Moreover, a correlation has been shown between Hgb, CRP, and pre-existing CVD, such that patients with pre-existing CVD are the most undernourished and anemic. This association could be the result of malnutrition–inflammation–arteriosclerosis (MIA) syndrome and its impact on refractory anemia and EPO resistance.

These results suggest that early-start PD reduces inflammation, avoids a deterioration in nutrition status, and potentially reduces the morbidity and mortality associated with advanced chronic kidney disease.

### Conclusions

A strong predictable association exists between RRF and inflammation and nutrition status in incident patients on PD. C-Reactive protein is a good marker for local–systemic inflammation and correlates well with nutrition status, anemia, and EPO responsiveness. In short-term follow-up, peritoneal transport type has no influence on RRF, inflammation, or nutrition status. Pre-existing CVD is associated with inflammation and anemia in these patients.

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